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Effects of the Hydrophobicity of the Reactants on Diels−Alder Reactions in Water

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To assess the importance of the hydrophobicity of different parts of diene and dienophile on the aqueous acceleration of Diels−Alder reactions, second-order rate constants have been determined for the reactions of cyclopentadiene (**1**), 2,3-dimethyl-1,3-butadiene (**4**), and 1,3-cyclohexadiene (**6**) with *N*-methyl-, *N*-ethyl-, *N*-propyl-, and *N*-butylmaleimide (**2a**−**d**) in different solvents. All these reactions are accelerated in water relative to organic solvents as a result of enhanced hydrogen bonding and enforced hydrophobic interactions during the activation process. The beneficial influence of water as compared to 1-propanol on the rate of the Diels−Alder reaction of **4** with **2a**−**d** increases linearly with the length of the alkyl chain of **2**. In contrast, for the reaction of both **1** and **6** with **2a**−**d**, no such effect was observed. This difference can be explained by a hydrophobic interaction between the methyl groups of **4** and the *N*-alkyl group of **2** during the activation process. In the reactions of **1** and **6**, lacking the methyl substituents, this interaction is not possible and elongation of the alkyl chain from ethyl onward does not result in an additional acceleration by water. The enhanced hydrophobicity near the reaction center of dienes **4** and **6** compared to **1** results in an increased aqueous acceleration of the Diels−Alder reactions of the former dienes with **2a**. These data indicate that an increase in the hydrophobicity close to the reaction center in the diene has a much more pronounced effect on the rate acceleration in water than a comparable increase in hydrophobicity in the dienophile further away from the reaction center. The Gibbs energies of transfer of initial state and activated complex of the Diels−Alder reactions under study have been determined. As expected, for all reactions the initial state in water is destabilized compared to that in 1-propanol. This destabilization becomes more pronounced when the nonpolar character of diene (close to the reaction center) or dienophile (distant from the reaction center) is increased. Likewise, an increase in the nonpolar character of **2** results in a destabilization of the activated complex. In contrast, addition of methyl or methylene units to the diene is *not* accompanied by a significant destabilization of the activated complex in water as compared to 1-propanol. We conclude that hydrophobic groups near the reaction center seem to lose their hydrophobic character completely in the activated complex of the Diels−Alder reaction, whereas more distant groups retain their nonpolar character throughout the reaction.

Introduction

The Diels−Alder reaction is an intensively used cycloaddition that enables the synthesis of complex polycyclic molecules with fine control over the stereochemistry. The mechanism of the Diels−Alder reaction has been subject of heated debate.[1] Nowadays it is generally accepted that the Diels−Alder reaction is a concerted process.[1] Diels−Alder reactions normally show small or modest solvent effects,[2] indicating a small change of polarity on going from initial state to activated complex. In 1980, however, Breslow discovered that Diels−Alder reactions performed in water can be subject to huge accelerations.[3] This observation led to increased interest from synthetic organic chemists in organic reactions in water. Soon it was discovered that other organic reactions, like the Claisen rearrangement,[4] the aldol condensation,[5] and the benzoin condensation[6] exhibit rate enhancements in water. To date, many more organic transformations have been carried out in water.[7]

Different explanations have been suggested for the rate enhancement of the Diels−Alder reaction in water. The first idea involved hydrophobic packing of the diene and dienophile,[8] but since intramolecular Diels−Alder reac-

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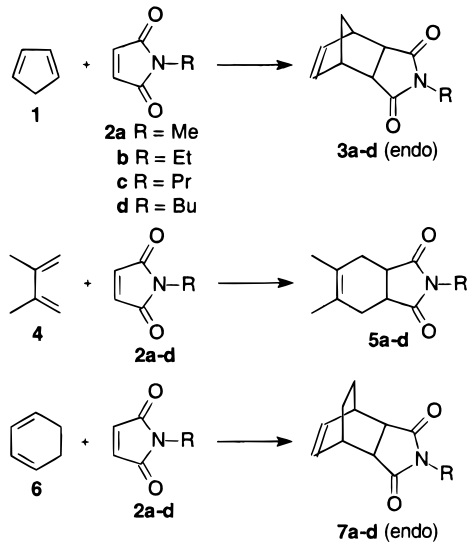
tions are also accelerated,[9] aggregation cannot be responsible for the aqueous acceleration. Moreover, vapor pressure measurements on the reactants of Diels−Alder reactions have indicated that no aggregation takes place at the concentrations used in kinetic experiments.[10] Alternatively, the solvent's internal pressure[11] and the cohesive energy density (CED)[11] have been used to explain rate enhancements of Diels−Alder reactions in water. Internal pressure is thought to reflect highly distance-dependent dispersion and dipole−dipole interactions within the solvent, and was proposed to influence the rate in the same way external pressure does.[12] Because the internal pressure of water is very low,[2c] this effect cannot account for the accelerating effect of water. In contrast, the CED reflects all intermolecular forces within a solvent and is related to the energy required to create a cavity in the solvent. The CED of the solvent has been successfully correlated with rate constants of some Diels−Alder reactions.[13] Also solvent polarity has been demonstrated to have a significant influence on the rate of some Diels−Alder reactions, but because correlations with solvent polarity parameters are usually poor,[13a,14] polarity alone cannot explain the aqueous acceleration. We have formulated the concept of "enforced hydrophobic interactions" as a major contributor to the acceleration of the Diels−Alder reaction in water.[9,10,15] The term "enforced" is used to stress that hydrophobic interactions occur simply because they are an integral part of the activation process. Also hydrogen bonding plays an important role,[16] probably in the same way as Lewis-acid catalysis does. Desimoni[17] found a hyperbolic relationship between the rate constants of Diels−Alder reactions and the acceptor number (AN)[18] of the solvent, stressing the importance of Lewis acid−Lewis base interactions consistent with hydrogen bond interactions. Recent research has been aimed at the problem of separating and quantifying the contributions of the enforced hydrophobic effect and the hydrogen bonding effect to the water-induced accelerations of Diels−Alder reactions. Recently we investigated the cycloaddition of cyclopentadiene to acridizinium bromide in which hydrogen bond interactions are of minor importance.[19] This reaction is only modestly accelerated in water. Computational methods also indicated that hydrogen bond interactions can be the dominant contribution to the rate enhancement in water.[16a−c,20]

In this paper we make an endeavor to provide further insight into the factors responsible for the enforced hydrophobic part of the acceleration of the Diels−Alder reaction in water. We report a kinetic investigation into the influence of the position of the hydrophobic groups with respect to the reaction center on the aqueous acceleration. For this purpose, the Diels−Alder reactions of a group of *N*-alkylmaleimides with a varying alkyl chain length (**2a**−**d**) with three different dienes, cyclopentadiene (**1**), 2,3-dimethyl-1,3-butadiene (**4**), and 1,3-cyclohexadiene (**6**), have been studied. Note that these reactants exhibit a variable hydrophobic character at sites close to (for the dienes) or distant from (in the case of the dienophiles) the reaction center.



Results and Discussion

Kinetic Data. The second-order rate constants for the Diels−Alder reactions of *N*-alkylmaleimides **2a**−**d** with dienes **1**, **4**, and **6** have been determined in water and in different organic solvents. The range of solvents was chosen as broad as possible (from *n*-hexane to water), including 1,1,1-trifluoroethanol (TFE), which is a solvent of strong hydrogen-bond donor capacity. Tables 1−3 show the results. In all cases the Diels−Alder reactions benefit dramatically from the use of water as the reaction medium. The aqueous acceleration approaches a factor of 1900 relative to *n*-hexane for the reaction between **4** and **2d**. The fact that all reactions are accelerated in TFE compared to other organic solvents strongly confirms the notion that hydrogen-bonding interactions also are an important contributor to the aqueous acceleration of Diels−Alder reactions.

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Table 1. Second-Order Rate Constants k_2 (M^{-1} s^{-1}) for the Diels–Alder Reactions of 1 with 2a–d in Different Solvents at 25 °C

solvent	2a	2b	2c	2d
n-hexane	4.75×10^{-2}	5.29×10^{-2}	4.18×10^{-2}	4.20×10^{-2}
acetonitrile	9.67×10^{-2}	1.26×10^{-1}	9.63×10^{-2}	9.84×10^{-2}
ethanol	3.02×10^{-1}	3.54×10^{-1}	2.76×10^{-1}	2.79×10^{-1}
l-propanol	3.51×10^{-1}	4.11×10^{-1}	3.24×10^{-1}	3.30×10^{-1}
TFE	4.31	5.04	3.83	3.85
water	14.2	21.6	16.8	18.1

Table 2. Second-Order Rate Constants k_2 (M^{-1} s^{-1}) for the Diels–Alder Reactions of 4 with 2a–d in Different Solvents at 25 °C

solvent	2a	2b	2c	2d
n-hexane	1.85×10^{-4}	1.03×10^{-4}	8.91×10^{-5}	8.56×10^{-5}
acetonitrile	4.39×10^{-4}	2.50×10^{-4}	2.08×10^{-4}	1.70×10^{-4}
ethanol	1.35×10^{-3}	7.23×10^{-4}	6.12×10^{-4}	5.22×10^{-4}
l-propanol	1.62×10^{-3}	8.24×10^{-4}	7.51×10^{-4}	7.55×10^{-4}
TFE	1.50×10^{-2}	7.80×10^{-3}	6.85×10^{-3}	6.84×10^{-3}
water	1.86×10^{-1}	1.49×10^{-1}	1.50×10^{-1}	1.61×10^{-1}

Table 3. Second-Order Rate Constants k_2 (M^{-1} s^{-1}) for the Diels–Alder Reactions of 6 with 2a–d in Different Solvents at 25 °C

solvent	2a	2b	2c	2d
ethanol	4.02×10^{-4}	3.22×10^{-4}	2.98×10^{-4}	2.83×10^{-4}
l-propanol	4.15×10^{-4}	4.19×10^{-4}	3.72×10^{-4}	3.69×10^{-4}
TFE	5.38×10^{-3}	5.99×10^{-3}	4.61×10^{-3}	4.82×10^{-3}
water	7.02×10^{-2}	1.05×10^{-1}	9.46×10^{-2}	1.10×10^{-1}

The aqueous accelerations relative to 1-propanol as the reaction medium for the reactions of **1**, **4**, and **6** with **2a–d** have been plotted in Figure 1. The Diels–Alder reactions of the more hydrophobic dienes **4** and **6** are significantly more accelerated in water than those of **1**. The increased hydrophobicity near the reaction center of the dienes **4** and **6** as compared to **1** is likely to be responsible for this difference.

In Figure 2 the aqueous accelerations ($k_{H_2O}/k_{1\text{-PrOH}}$) of the Diels–Alder reactions of the dienes **1**, **4**, and **6** with dienophiles **2a–d**, normalized to the reactions of these dienes with **2a**, are plotted against the length of the alkyl chain of **2**. Interestingly, the accelerations of the reactions of **4** reveal an approximately linear trend with increasing alkyl chain length. In contrast, the reactions of **1** and **6** with **2a–d** demonstrate that elongation of the alkyl chain of **2** from ethyl onward has no significant influence on this acceleration. This difference can be rationalized by considering the activated complexes of the Diels–Alder reactions (Figure 3). The Diels–Alder reactions under study yield predominantly *endo*-cycloadduct, so that only the *endo*-activated complexes need to be considered. The *endo*-activated complexes of the Diels–Alder reactions of **4** with **2a–d** clearly reveal a possibility for hydrophobic interactions of the *N*-alkyl group of **2** with the methyl groups of **4**. During the activation process the hydrophobic hydration spheres of the *N*-alkyl group of **2** and those of the two methyl groups of **4** will overlap. This destructive overlap gives an additional enforced hydrophobic effect, resulting in an enhanced aqueous acceleration. A similar additional interaction is not possible for Diels–Alder reactions of dienes **1** and **6** with **2a–d**.

A quantitative comparison of the effect of increased hydrophobicity distant from the reaction center with the effect of increased hydrophobicity closer to the reaction center can be made by examining Figures 1 and 2. These figures show that k_{H_2O}/k_{1-PrOH} for the reaction of **4** with **2d** is only a factor two larger than k_{H_2O}/k_{1-PrOH} for the reaction of **4** with **2a**. This effect is caused by elongation of the *N*-alkyl group of **2** with three methylenes at a site distant from the reaction center. Figure 1 shows that k_{H_2O}/k_{1-PrOH} for the Diels–Alder reactions of dienes **4** and **6** with **2a** are about a factor three larger than k_{H_2O}/k_{1-PrOH} for the corresponding reaction of diene **1**. Dienes **4** and **6** are more hydrophobic than diene **1** due to the presence of approximately one additional methylene group. This group is located close to the reaction center. Apparently, hydrophobicity near the reaction center has a larger influence on the aqueous accelerations than hydrophobicity distant from the reaction center.

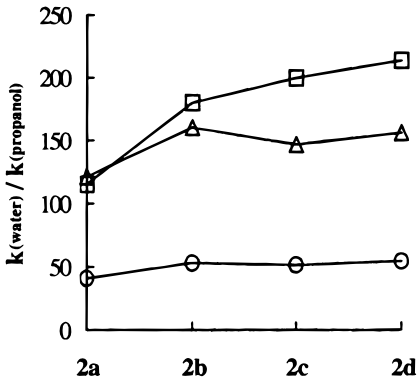

Figure 1. Accelerations of the Diels–Alder reactions of **1** (○), **4** (□), and **6** (△) with **2a–d** in water, compared to 1-propanol.

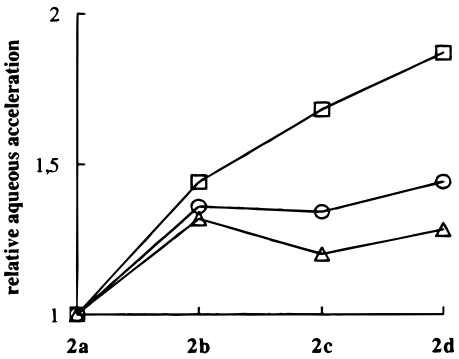

Figure 2. Relative aqueous accelerations ($k_{water}/k_{1\text{-PrOH}}$), normalized to the acceleration of the reaction with **2a,** for the reactions of **1** (○) and **4** (□) with **2a–d** relative to *n*-hexane, and for the reaction of **6** (△) with **2a–d** relative to 1-propanol.

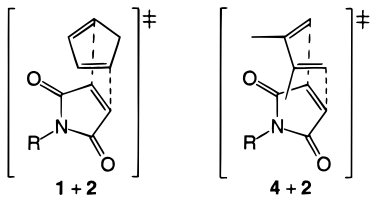

Figure 3. *Endo*-activated complexes of the Diels–Alder reactions of **1** and **4** with **2**.

Gibbs Energies of Transfer. It would be informative to have access to the relative Gibbs energies of the initial states and the activated complexes in different solvents. Therefore, we have determined the Gibbs energies of transfer of the initial states of the Diels–Alder reactions of dienes **1** and **4** with dienophiles **2a** and **2b** from 1-propanol to water using vapor pressure measurements.

Table 4. Gibbs Energies of Transfer (kJ·Mol^{-1}) for 1, 4, and 2a,b from 1-Propanol to Water at 25 °C

1	4	2a	2b
8.92	11.5	0.74	3.26

Table 5. Gibbs Energies of Activation $\Delta^{\ddagger}G°$ (kJ·Mol^{-1}) for the Reactions of 1 and 4 with 2a,b in 1-Propanol and Water at 25 °C

solvent	1 + 2a	1 + 2b	4 + 2a	4 + 2b
1-propanol	75.6	75.2	88.9	90.6
water	66.4	65.4	77.1	77.7

The results are summarized in Table 4. From these data and the Gibbs energies of activation (Table 5), the relative Gibbs energies of transfer for the activated complexes can be calculated. Figure 4 shows the results from which a number of conclusions can be drawn.

First of all, invariably the initial states in water are destabilized relative to those in 1-propanol. This destabilization is much less pronounced for the activated complexes and in some cases almost vanishes. Similar results have been observed previously for the Diels–Alder reaction between methyl vinyl ketone and **1**.[10,15c,16d]

Furthermore, a comparison of the initial and transition states of the Diels–Alder reactions of diene **1** with the dienophiles **2a** and **2b**, respectively, and a comparison of the corresponding data for the reactions of diene **4** with the same dienophiles provides information about the influence of the hydrophobicity distant from the reaction center. Figure 4 indicates that the transfer of the initial state of the reaction of **2b** with **1** from 1-propanol to water is 2.5 kJ·mol^{-1} more unfavorable than the corresponding transfer of the initial state of the reaction of **2a** with **1** (compare C with B). The enhanced hydrophobicity of the distant alkyl group in **2b** compared to that in **2a** is responsible for the increased initial state destabilization. This value is typical for transfer of one methylene unit from 1-propanol to water.[21] The transfer of the activated complex of the reaction of **2b** with **1** from 1-propanol to water is 1.9 kJ·mol^{-1} more unfavorable than the corresponding transfer for the activated complex of the reaction of **2a** with **1** (compare G with F). The increased hydrophobicity of the distant alkyl group in **2b** compared to that in **2a** is responsible for this difference. Hence, for Diels–Alder reactions of diene **1**, the hydrophobic destabilization due to elongation of the alkyl chain in the dienophile by one methylene group has comparable effects on the initial and the transition state.

For the reactions of **2a** and **2b** with **4** a similar picture emerges. The transfer of the initial state of the reaction of **2b** with **4** from 1-propanol to water is 2.5 kJ·mol^{-1} more unfavorable than the corresponding transfer of the initial state of the reaction of **2a** with **4** (compare D with A). Again, the increased hydrophobicity of the distant alkyl group in **2b** compared to that in **2a** is responsible for this difference. The transfer of the activated complex of the reaction of **2b** with **4** from 1-propanol to water is 1.4 kJ·mol^{-1} more unfavorable than the corresponding transfer of the activated complex of the reaction of **2a** with **4** (compare H with E). This can be attributed to the increased hydrophobicity of the distant alkyl group in **2b** compared to that in **2a**. In summary, for the Diels–Alder reactions of dienes **1** and **4** with **2a–b**, elongation of the alkyl chain in the dienophile by one methylene group has a comparable effect on the Gibbs energies of transfer of the initial and the activated complex from 1-propanol to water. Hence, the additional methylene group contributes only to a minor extent to the aqueous rate enhancement.

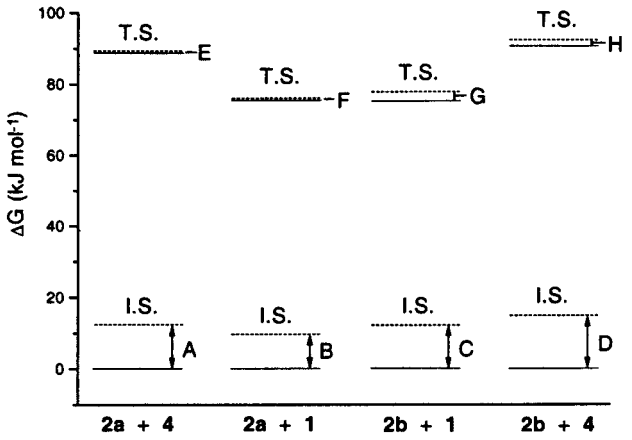

Figure 4. Gibbs energy diagram of the Diels–Alder reactions of **1** and **4** with **2a** and **2b** in 1-propanol (—) and water (- - -).

Finally and most interestingly, a comparison of the initial and transition states for the reactions of **2a** with dienes **1** and **4**, respectively, provides information about the influence of the hydrophobicity close to the reaction center of the diene. Figure 4 demonstrates that the transfer of the initial state of the reaction of **4** with **2a** from 1-propanol to water is 2.6 kJ·mol^{-1} more unfavorable than the corresponding transfer of the initial state of the reaction of **1** with **2a** (compare A with B). This difference is a result of the increased hydrophobicity of **4** as compared to that of **1**. The transfer of the activated complex of the reaction of **4** with **2a** from 1-propanol to water is, within experimental error, equal to the corresponding transfer of the activated complex of the reaction of **1** with **2a** (compare E with F). Apparently, the enhanced hydrophobic character of **4** relative to **1** in the initial state has completely vanished in the activated complex. Hence, the additional hydrophobic groups in **4** contribute maximally to the acceleration in water.

We conclude that the hydrophobic contribution to the acceleration of the Diels–Alder reaction in water is not so much a result of a reduction of solvent accessible surface area, but rather a consequence of the *complete disappearance* of the hydrophobic character of the different groups near the reaction center in the dipolar and more strongly hydrated activated complex.

Conclusions

The Diels–Alder reactions of cyclopentadiene **1**, 2,3-dimethyl-1,3-butadiene **4**, and 1,3-cyclohexadiene **6** with *N*-alkylmaleimides **2a–d** are accelerated in water relative to organic solvents. The acceleration is due to both hydrogen bonding of water to the polarized activated complex and to enforced hydrophobic interactions between the reactants. The aqueous acceleration of the reactions of **4** with **2a–d** depend linearly on the alkyl chain length, contrary to the results obtained for the corresponding reaction of dienes **1** and **6**. This difference can be explained by overlap of hydrophobic hydration spheres of the methyl groups of **4** and of the *N*-alkyl group of **2** during the activation process. This overlap is

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not possible for the reactions of **1** and **6** with **2**. Apparently, hydrophobic groups distant from the reaction center can give an additional aqueous acceleration when these hydrophobic groups approach other nonpolar parts of the reacting system during the reaction. The acceleration of the Diels−Alder reactions of the dienes **4** and **6** with **2** upon going from 1-propanol to water is more pronounced than the corresponding acceleration of the reaction of **1** with **2**. This difference can be attributed to the increased hydrophobicity near the reaction center of **4** and **6** as compared to **1**. Comparing the effect of increased hydrophobicity distant from the reaction center with the effect of increased hydrophobicity closer to the reaction center demonstrates that the latter has a larger influence on the aqueous acceleration than the former. These interpretations are supported by the Gibbs energies of transfer, which indicate that enhanced hydrophobic character distant from the reaction center is only partially diminished in the activation process, whereas enhanced hydrophobic character closer to the reaction center completely disappears in the activation process.

We contend that the hydrophobic part of the acceleration of the Diels−Alder reaction in water is not so much a result of a reduction of solvent accessible surface area, but rather a consequence of the complete disappearance of hydrophobic character of the different groups near the reaction center in the activated complex.

Experimental Section

Materials. Cyclopentadiene (**1**) was prepared from its dimer (Merck-Schuchardt) immediately before use by cracking over a platinum wire. 2,3-Dimethyl-1,3-butadiene (**4**) and 1,3-cyclohexadiene (**6**) were obtained from Aldrich and purified by distillation. *N*-Methylmaleimide (**2a**) was purchased from Aldrich and crystallized from ether. *N*-Ethylmaleimide (**2b**) was obtained from Janssen Chimica and crystallized from ether. *N*-Propyl- and *N*-butylmaleimide (**2c,d**) were synthesized according to the literature.[22] Demineralized water was distilled twice in a quartz distillation unit. 1-Propanol, acetonitrile, and 1,1,1-trifluoroethanol were distilled before use. Ethanol and *n*-hexane were of the highest purity available.

Kinetic Measurements. Second-order rate constants for the Diels−Alder reactions performed in organic solvents and for the reactions of **4** and **6** with **2a**−**d** in water were determined using UV−vis spectroscopy (Perkin-Elmer λ2, 5, or 12). The disappearance of the absorption of the dienophile was monitored at $\lambda_{max} = 298$ nm (25.0 ± 0.1 °C). The reactions performed in organic solvents were followed using procedures described earlier.[9] The rates of the reactions of **4** and **6** with **2a**−**d** in water were determined using initial rate kinetics.[23] The second-order rate constants for the reaction of **1** with **2a**−**d** were determined using an SX17MV stopped-flow apparatus. All rate constants were measured at least three times. Those for the reactions involving **1** and **4** were reproducible to within 3%, whereas those for reactions involving **6** showed a reproducibility of 6%. The initial rate method gave a reproducibility of 5%, and the stopped-flow method gave 3% reproducibility.

Gibbs Energies of Transfer. The Gibbs energy of transfer of a solute from one solvent to another was determined from the vapor pressures of the solute for the different solvents by using the equation:

$$\Delta G_{\text{transfer}}\,(\mathbf{1} \rightarrow \mathbf{2}) = -RT \ln\left(\frac{p(\mathbf{1})m(\mathbf{2})}{p(\mathbf{2})m(\mathbf{1})}\right)$$

where $m(i)$ is the molality of the solute in solvent i and $p(i)$ is the vapor pressure of the solute in that solution.[10,24] The vapor pressures were obtained from GC peak areas. The measurements were carried out in 5 mL round-bottomed flasks using 3 mL of solution (concentrations ranging from 1×10^{-1} M to 1×10^{-3} M for 1-propanol, and from 5×10^{-3} M to 4×10^{-4} M for water). The flasks were sealed with a rubber septum cap and placed in a thermostated water bath at 25.0 ± 0.1 °C. The solutions were stirred continuously. A small needle was placed in the septum cab to maintain atmospheric pressure in the flask. For each solute in each solvent, the vapor pressures were determined for at least five different concentrations. For each concentration, 200 μL of the vapor above the solution was chromatographed at least three times, using a Hewlett-Packard 5890A gas chromatograph, equipped with a HP1 cross-linked methyl silicone gum column (15 m × 0.53 mm × 2.65 μm film thickness). The detection temperature was set at 180 °C. The column and injection temperature varied for every compound and solvent in order to get a suitable retention time. The peak areas of the compounds were determined by integration. For dienes **1** and **4**, the peak areas were reproducible to within 5%. For the other solutions, peak areas were reproducible to within 3%. Plots of the vapor pressures versus the molalities were linear, indicating that the solutions can be regarded as thermodynamically ideal. The slopes of the plots, providing the Henry constant, were calculated using a least-squares method and were subsequently used for the calculation of the Gibbs energies of transfer.

Product Analysis. A solution of diene (2.0×10^{-3} M for **1** and **6** and 1.5×10^{-3} M for **4**) and dienophile (6×10^{-4} M) in demineralized water (1 L) was stirred at room temperature until the UV-absorption of the dienophile had disappeared. The reaction mixture was extracted three times with 100 mL of chloroform. The chloroform layer was washed with a saturated NaCl solution and dried over magnesium sulfate. After evaporation of the chloroform, the products were obtained in quantitative yields and almost always as oils. The products were crystallized from petroleum ether (40−60) and analyzed. The ^{1}H NMR chemical shifts (relative to TMS) of the products were recorded in $CDCl_3$ using a Varian 200 MHz NMR spectrometer. The melting points were measured on a Mettler FP52 melting point apparatus.

***endo*-*N*-Methylbicyclo[2.2.1]hept-5-ene-2,3-dicarboximide (3a):** mp 106.2−106.9 °C; ^{1}H NMR ($CDCl_3$) δ 1.65 (m, 2H), 2.82 (s, 3H), 3.27 (m, 2H), 3.39 (m, 2H), 6.10 (s, 2H). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.77; H, 6.26; N, 7.91. Found: C, 67.66; H, 6.33; N, 7.93.

***endo*-*N*-Ethylbicyclo[2.2.1]hept-5-ene-2,3-dicarboximide (3b):** mp 78.0−78.7; ^{1}H NMR ($CDCl_3$) δ 1.03 (t, 3H), 1.65 (m, 2H), 3.24 (m, 2H) 3.39 (m, 2H), 3.39 (q, 2H), 6.09 (s, 2H). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.02; H, 6.86; N, 7.33.

***endo*-*N*-Propylbicyclo[2.2.1]hept-5-ene-2,3-dicarboximide (3c):** mp 76.0−76.5 °C; ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 3H), 1.36 (m, 2H), 1.63 (m, 2H), 3.24 (m, 2H), 3.28 (t, 2H), 3.38 (m, 2H), 6.09 (s, 2H). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.25; H, 7.35; N, 6.85.

***endo*-*N*-Butylbicyclo[2.2.1]hept-5-ene-2,3-dicarboximide (3d):** mp 43.5−44.1 °C; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H), 1.25 (m, 2H), 1.39 (m, 2H), 1.63 (m, 2H), 3.23 (m, 2H), 3.32 (t, 2H), 3.38 (m, 2H), 6.09 (s, 2H). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.29; H, 7.73; N, 6.45.

1,2,*N*-Trimethylcyclohex-1-ene-4,5-dicarboximide (5a): mp 74.7−75.3 °C; ^{1}H NMR ($CDCl_3$) δ 1.66 (s, 6H), 2.33 (m, 4H), 2.94 (s, 3H), 3.03 (t, 2H). Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.29; H, 7.82; N, 7.26.

1,2-Dimethyl-*N*-ethylcyclohex-1-ene-4,5-dicarboximide (5b): mp 60.8−61.7 °C; ^{1}H NMR ($CDCl_3$) δ 1.06 (t, 3H),

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1.65 (s, 6H), 2.32 (m, 4H), 3.00 (t, 2H), 3.49 (q, 2H). Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.09; H, 8.27; N, 6.67.

1,2-Dimethyl-*N*-propylcyclohex-1-ene-4,5-dicarboximide (5c): mp 36.5−37.8 °C; ^{1}H NMR ($CDCl_3$) δ 0.81 (t, 3H), 1.51 (q, 2H), 1.65 (s, 6H), 2.33 (m, 4H), 3.00 (t, 2H), 3.42 (t, 2H). Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.54; H, 8.66; N, 6.31.

***N*-Butyl-1,2-dimethylcyclohex-1-ene-4,5-dicarboximide (5d):** mp 27.6−29.6 °C; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.20 (m, 2H), 1.47 (m, 2H), 1.65 (s, 6H), 2.33 (m, 4H), 3.00 (t, 2H), 3.45 (t, 2H). Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 70.05; H, 9.07; N, 5.62.

***endo*-*N*-Methylbicyclo[2.2.2]oct-2-ene-5,6-dicarboximide (7a):** mp 124.3−125.4 °C; ^{1}H NMR ($CDCl_3$) δ 1.49 (m, 4H), 2.83 (t, 2H), 2.88 (s, 3H), 3.15 (m, 2H), 6.15 (q, 2H). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6,85; N, 7.32. Found: C, 68.93; H, 6.85; N, 7.35.

***endo*-*N*-Ethylbicyclo[2.2.2]oct-2-ene-5,6-dicarboximide (7b):** mp 125.8−126.8 °C; ^{1}H NMR ($CDCl_3$) δ 1.06 (t, 3H), 1.49 (m, 4H), 2.80 (t, 2H), 3.15 (m, 2H), 3.45 (q, 2H), 6.15 (q, 2H). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.09; H, 7.42; N, 6.87.

***endo*-*N*-Propylbicyclo[2.2.2]oct-2-ene-5,6-dicarboximide (7c):** mp 100.3−101.3 °C; ^{1}H NMR ($CDCl_3$) δ 0.84 (t, 3H), 1.49 (m, 4H), 1.50 (m, 2H), 2.81 (t, 2H), 3.14 (m, 2H), 3.36 (t, 2H), 6.16 (q, 2H). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 70.95; H, 7.76; N, 6.35.

***endo*-*N*-Butylbicyclo[2.2.2]oct-2-ene-5,6-dicarboximide (7d):** mp 57.1−57.8 °C; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.25 (m, 2H), 1.44 (m, 2H), 1.49 (m, 4H), 2.80 (t, 2H), 3.39 (t, 2H), 6.15 (q, 2H). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.10; H, 8.25; N, 6.08.

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